

**Patent Claims:**

1. A bispecific antibody, or a fragment thereof, having the capability to bind to different epitopes located on same or different ErbB receptor molecule types, said antibody comprising a first antigen-binding site that binds to an epitope of a first receptor type, which is ErbB1, and a second different antigen-binding site that binds to a different epitope of a second ErbB receptor molecule type.  
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2. A bispecific antibody according to claim 1, wherein said second ErbB receptor molecule type is ErbB1 (EGFR).  
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3. A bispecific antibody according to claim 1, wherein said second ErbB receptor molecule type is ErbB2 (Her-2).  
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4. A bispecific antibody according to any of the claims 1 – 3, wherein at least one of said epitopes is located within the receptor binding domain.
5. A bispecific antibody of claim 4, wherein said receptor binding domain is the binding domain of the natural ligand(s) of said ErbB receptor.  
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6. A bispecific antibody according to any of the claims 1 – 3, wherein the first or second antigen binding site binds to an epitope within the binding domain of the natural ligand(s) of said ErbB receptor molecule type.
7. A bispecific antibody according to any of the claims 1 – 3, wherein the first and second antigen binding site binds to an epitope within the binding domain of the natural ligand(s) of said ErbB receptor molecule type.  
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8. A bispecific antibody according to any of the claims 1 – 7, wherein the antigen binding sites bind to different epitopes which are located on the same ErbB receptor molecule type.  
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9. A bispecific antibody according to any of the claims 1 – 7, wherein the antigen binding sites bind to different epitopes which are located on different ErbB receptor molecule types.
- 5       10. A bispecific antibody of claim 8, wherein the first and second antigen binding site binds each to a different epitope within the binding domain of the natural ligand of said ErbB receptor, thus blocking and / or inhibiting the receptor, whereby blocking and / or inhibition of the ErbB receptor, and induction of down-regulation of ErbB receptor-specific pathway signaling is enhanced as compared with the respective monospecific antibody.
- 10      11. A bispecific antibody of claim 9, wherein induction of crosslinking and / or dimerization of different ErbB receptor molecules having the same or different specificity, is enhanced as compared with binding of the bispecific antibody to epitopes on the same ErbB receptor molecule..
- 15      12. A bispecific antibody according to any of the claims 1 – 11, wherein said first antigen-binding site derives from humanized, chimeric or murine MAb 425.
- 20      13. A bispecific antibody according to any of the claims 1 – 11, wherein said first antigen-binding site derives from humanized, chimeric or murine MAb 225.
- 25      14. A bispecific antibody according to claim 12 or 13 designated as "BAb <h425, c225>", wherein said first antigen-binding site derives from humanized, chimeric or murine MAb 425, and said second antigen-binding site derives from humanized, chimeric or murine MAb 225, and each antigen-binding site binds to a different epitope on the ErbB1 receptor (EGFR) molecule.
- 30      15. A bispecific antibody of claim 14, wherein said different epitopes are located within the binding domain of the natural ligand(s).
16. A bispecific antibody according claim 12 or 13, wherein the second antigen binding site binds to a ErbB2 receptor molecule (Her-2) or a VEGF receptor molecule.

17. A bispecific antibody of claim 16, wherein said second antigen-binding site derives from MAb 4D5 (Herceptin®).

5        18. A bispecific antibody fragment deriving from a bispecific antibody as defined in any of the claims 1 – 17, wherein the fragment is F(ab')2.

10        19. An immunoconjugate comprising a bispecific antibody according to any of the claims 1 – 18 or a fragment thereof, fused directly or via a linker molecule via its C-terminus to a biologically effective protein, polypeptide or peptide.

15        20. An immunoconjugate of claim 19, wherein said protein is a cytokine.

21. A pharmaceutical composition comprising a bispecific antibody or an immunoconjugate as specified in any of the claims 1 – 20, optionally together with a pharmaceutically acceptable carrier, diluent or excipient.

22. A pharmaceutical composition of claim 21, further comprising a monospecific anti-ErbB antibody or a functionally effective fragment thereof.

20        23. A pharmaceutical composition of claim 22, wherein said monospecific anti-ErbB antibody or a functionally effective fragment thereof is selected from the group consisting of MAb 425, MAb 225, or MAb 4D5 (Herceptin®).

25        24. A pharmaceutical composition according to any of the claims 21 – 23, additionally comprising a cytotoxic agent.

25        25. A pharmaceutical composition according to claim 24, wherein said cytotoxic agent is a chemotherapeutic agent.

30        26. A pharmaceutical composition according to claim 25, wherein said chemotherapeutic agent is selected from any of the compounds of the group: cisplatin, doxorubicin, gemcitabine, docetaxel, paclitaxel, bleomycin.

27. A pharmaceutical composition of claim 24, wherein said cytotoxic agent is an ErbB receptor inhibitor, a VEGF receptor inhibitor, a tyrosine kinase inhibitor, a protein kinase A inhibitor, an anti-angiogenic agent, an anti-hormonal agent, or a cytokine.

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28. A pharmaceutical kit comprising

- (i) a first package comprising at least a bispecific antibody or an immunoconjugate, as specified in any of the claims 1 to 20, and
- (ii) a second package comprising at least a monospecific anti-ErbB antibody or a functionally effective fragment thereof.

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29. A pharmaceutical kit according to claim 28 comprising a first package that comprises bispecific antibody "BAb <h425, c225>" or its F(ab')2 fragment, and a second package comprising humanized MAb 425 (h425), chimeric MAb 225 (c225) or humanized MAb 4D5 or functionally effective antibody fragments thereof.

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30. A pharmaceutical kit according to claim 28 or 29 comprising additionally a third package comprising a cytotoxic drug.

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31. A pharmaceutical kit according to claim 30, wherein said cytotoxic drug is selected from any of the compounds of the group: cisplatin, doxorubicin, gemcitabine, docetaxel, paclitaxel, bleomycin, an ErbB receptor inhibitor, a VEGF receptor inhibitor, a tyrosine kinase inhibitor, a protein kinase A inhibitor, an anti-hormonal agent, or an anti-angiogenic agent.

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32. Use of a bispecific antibody or a pharmaceutical composition / kit as defined in any of the claims 1 – 31, for the manufacture of a medicament for the treatment of tumors and tumor metastases and related diseases that overexpress ErbB receptors.

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